A Study to Evaluate the Effectiveness, Pharmacokinetics, Safety, and Acceptability of Sayana® Press when Injected Every Four Months

FHI 360 Study Number 926400

Statistical Analysis Plan, Version 3.0

STATISTICAL ANALYSIS PLAN APPROVAL

Study No.: 926400

Study Title: A Study to Evaluate the Effectiveness, Pharmacokinetics, Safety, and Acceptability of Sayana® Press when Injected Every Four Months

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On behalf of Mario Chen, Director of Biostatistics

FHI 360

STUDY SUMMARY

Title:	A Study to Evaluate the Effectiveness, Pharmacokinetics, Safety, and Acceptability of Sayana® Press when Injected Every Four Months
FHI 360 Study #:	926400
Design:	Randomized, multi-center, parallel-group study
Investigational Drug:	Sayana® Press (medroxyprogesterone acetate injectable suspension, 104 mg/0.65 mL)
Active Ingredient:	Medroxyprogesterone acetate (MPA)
Phase of Study:	3
Number of Centers[1]:	3
Countries Planned:	Brazil, Chile, and Dominican Republic
Study Duration:	Recruitment is expected to take 9 months and each participant will be followed for 12 months of product use. The total study duration is anticipated to be 33 months, including initiation activities, analysis, and reporting.
Study Population:	A total of 750 healthy, sexually active women between 18 and 35 years of age who are willing to use Sayana® Press injected every 4 months as their only means of contraception for 12 months.
Primary Objective:	To evaluate the effectiveness of Sayana® Press injected subcutaneously every 4 months in the abdomen or upper thigh for 12 months (3 treatment cycles) of use.
Primary Endpoint:	Pregnancy
Secondary Objectives:	1) To assess trough concentrations, accumulation and apparent terminal half-life of MPA, and the impact of subcutaneous injection site (abdomen, upper thigh, or back of the upper arm) on these parameters, when Sayana® Press is injected every 4 months for 12 months of use; 2) To evaluate the safety of Sayana® Press when injected every 4 months for 12 months of use; 3) To evaluate the acceptability of Sayana® Press when injected every 4 months for 12 months of use.
Secondary Endpoints:	Serum MPA concentrations on day 0 (baseline), months 2, 3, 4, 8, and 12 after treatment initiation (subset of 120 participants, only); serious adverse events and adverse events leading to product withdrawal; injection site reactions (ISR), bleeding patterns, blood pressure, and body weight; and responses to acceptability questions.

[1] The protocol refers to the three locations where the study will take place as study sites. This document will refer to them as centers to avoid confusion with the randomized injection sites.

Exploratory Objective: To evaluate return to ovulation among a subset of study participants who received month 4 and month 8 injections and plan to use non-hormonal methods of contraception, or no contraception, for up to a maximum of 12 months from the last study injection.

Exploratory Endpoint: Return to ovulation, where ovulation is defined as a single elevated serum progesterone (P ≥4.7 ng/mL) or a confirmed pregnancy test.

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I. Introduction

This statistical analysis plan (SAP) is an expanded version of the summary analysis plan included in the protocol (v8.0-B) approved by the FHI 360 PHSC on 4 February 2020. Any significant changes made to this plan after study initiation (including those made to address revisions to the protocol) will be documented in an Appendix and using footnotes. Mock tables, figures and listings (TFLs) designed to capture the results of analyses will be approved by the Study Director prior to any un-blinding.

II. Study Design and Procedures

This is a three-arm, randomized, partially blinded, multi-center, parallel-group study to evaluate the effectiveness, pharmacokinetics (PK), safety, and acceptability of Sayana® Press when injected every 4 months (17-18 weeks) for 3 treatment cycles (12 months) of use. A total of 750 healthy, sexually active women aged 18 to 35 years with regular menstrual cycles and no DMPA use in the previous 12 months will be enrolled and followed for pregnancy. Among all enrolled, 710 will be randomized to receive subcutaneous (SC) injections in the abdomen or upper thigh in accordance with the PATH Sayana injection instructions, which are consistent with prescribing information, for the primary effectiveness analysis. An additional 40 women will be randomized to receive SC injections in the back of the upper arm to assess whether differences in PK may exist which could impact the grace period for reinjections for that injection site.

Treatment will begin in the first 5 days of menses. A single MPA serum sample will be collected from all participants at baseline. All participants will be scheduled to receive re-injections at month 4 (approximately 17 weeks after treatment initiation) and month 8 (approximately 35 weeks after treatment initiation) and complete their planned follow-up at month 12 (approximately 53 weeks after treatment initiation). There will be a plus 7-day grace period for re-injections, but women who are up to 28 days late may continue treatment if they have a negative urine pregnancy test. Urine pregnancy testing will be performed at month 4, at study exit, at month 8 if the participant is more than 7 days late for her visit, and at any time during the study if clinically indicated. Participants will be evaluated for injection site reactions and asked to provide information on adverse events, prohibited concomitant medications and other contraceptive use, vaginal bleeding, and method acceptability at months 4, 8 and 12. Information on adverse events and use of any prohibited concomitant medications will be recorded if reported by participants at month 2 and 3 PK visits and at any unscheduled visits.

III. General Analytic Considerations

A. Study Size and Power

The sample size of 710 women receiving injections in the abdomen or upper thigh is expected to be sufficient to ensure that the difference between the estimated Pearl Index (pregnancies per 100 woman-years of use) and the corresponding upper 95% confidence bound does not exceed 1.0, so long as the observed Pearl Index is less than 0.75 and at least 80% of participants complete 12 months of follow-up. (The study has a 90% chance of achieving this precision target if the true (unobserved) pregnancy rate is no more than 0.5 per 100 women-years). In

addition, a cohort of 120 women (40 receiving injections in each the abdomen, upper thigh, and back of the upper arm) is sufficient to provide 85% power to detect 30% relative differences in PK parameters between injection sites, assuming the coefficient of variation is no more than 40% and using two-sided 0.05 level significance tests.

B. Data Source

Data management (DM) plans are detailed in a separate study-specific document. Briefly, study center data are recorded on paper case report forms (CRFs) which are scanned by the study centers and entered into a clinical database management system at FHI 360. Data will be verified by study monitors and appraised for consistency by FHI 360 DM staff using both automated logical checks and manual review. A trained medical coder at FHI 360 will code all SAEs, AEs leading to product withdrawal, and AEs that are Grade 1 or higher ISRs using the Medical Dictionary for Regulatory Activities (MedDRA). Any adjudication of estimated dates of fertilization or other endpoint data will be performed following FHI 360 Standard Operating Procedures (SOPs). A central laboratory (PPD Development) will perform serum MPA testing, with results transferred to FHI 360 DM via password-protected Excel files. FHI 360 DM will create SAS datasets (version 9.4 or higher) containing lab and CRF data for use by biostatisticians conducting interim and final analyses.

C. Missing Data

It is anticipated that some event dates required for safety analyses may be incomplete. Decision rules for how and when to impute such incomplete date fields will be developed and documented by the medical monitor when reviewing study data and be documented in any study report produced. All other missing data will be ignored (i.e., treated as missing at random) unless patterns are identified through exploratory analysis which suggest the potential for biased assessments of efficacy, safety, PK, or acceptability. In the event such patterns are identified, rules for imputing data will be clearly described and justified in the study report.

D. Covariate Adjustment

The primary efficacy analysis will adjust for study center through stratification. Any other adjustments for covariates are addressed in the relevant sections below.

E. Test Size and Confidence Levels

Unless otherwise noted, all confidence intervals reported for the primary, secondary, and subgroup analyses will be computed at the 95% coverage level, and all p-values will be assessed at the two-sided 0.05 significance level, with no adjustment for multiple testing.

IV. Randomization, Allocation Concealment, and Blinding

A. Randomization

All participants will receive the same study drug, Sayana® Press, and will be randomized to receive their injections in one of three subcutaneous injection sites: abdomen, upper thigh, or back of the upper arm. One cohort of N=630 will be randomized 1:1 to receive their subcutaneous injections of Sayana® Press in the abdomen or upper thigh, and a second PK cohort of N=120 women who agree to serum MPA testing at 6 time points (baseline and

months 2, 3, 4, 8, and 12) will be randomized 1:1:1 to receive their injections in the abdomen, upper thigh, or back of the upper arm. Using this randomization scheme, 355 women will receive their injections in the abdomen, 355 in the upper thigh, and 40 in the back of the upper arm. Randomization in each cohort will use randomly-permuted blocks, stratified by study center and cohort with the following planned enrollment totals at each site: 250 at the center in Brazil (UNICAMP), 150 at the center in Chile (ICMER), and 350 at the center in the Dominican Republic (Profamilia). Within these totals, 42 at Profamilia, 36 at ICMER, and 42 at UNICAMP will be randomized in the PK cohort and the remainder of the enrollment total at each center will be randomized in the primary cohort. Randomization sequences will be created for each combination of study center and cohort by an FHI 360 Randomization Statistician using a validated program written in SAS® version 9.4 or higher. Recognizing that actual numbers of participants enrolled at each site may change during the enrollment period due to center performance or other issues, additional randomization numbers will be generated for the primary cohort within each center to allow one or two centers to expand enrollment to compensate for reduced enrollment at the remaining center(s)[2].

B. Allocation Concealment

Treatment assignments will be concealed within sealed, opaque, sequentially numbered randomization envelopes provided to each study center. Each envelope will have the randomization number printed on the outside, with the corresponding SC injection site assignment concealed within. The randomization envelopes will be maintained in a secure location at each study center, with access limited to authorized personnel per center-specific study procedures. Trained center staff will open the next available envelope (from the appropriate sequence of envelopes based on which cohort the participant consented to), and allocate the next treatment assignment, only after a participant has been confirmed to be eligible, consented to participate, and undergone all other enrollment procedures, including having a blood sample collected for MPA testing among women agreeing to participate in the PK cohort.

C. Blinding

Since this study is not randomizing study drug but rather site of SC injection, neither participants nor center staff will be blinded. However, laboratory staff analyzing serum MPA specimens and staff at FHI 360 responsible for adjudicating pregnancy outcomes and coding adverse events will be blinded to individual participant injection site assignments for the duration of each participant's follow up. Other FHI 360 staff may review interim PK data, including MPA concentrations of any women who become pregnant, to inform other FHI 360 MPA projects (see DSMB Operational Plan for details on timing of any un-blinded review of PK data).

[2] In September 2018, 100 of the planned enrollment total for UNICAMP, Brazil were shifted to Profamilia, DR due to study timelines and slower than expected enrollment at the UNICAMP center.

V. Analysis Populations and Analysis Sets

In the below definitions, an Analysis Population refers to a particular set of participants and an Analysis Set defines the time contributed to analyses by participants in a given Population. Additional censoring rules for analyses based on these sets are described in relevant sections.

A. Treated Population

The Treated Population consists of all enrolled participants who receive a dose of study drug. Unless noted otherwise, all analyses based on this population will be performed per intention-to-treat principles, ignoring any randomization errors, allocation errors, or the receipt of injections during follow-up that differ from the baseline injection site.

i. Safety Analysis Set

The Safety Analysis Set includes all follow up time contributed by each participant in the Treated Population, including time in the 8-28 day 'late' period for reinjections or final visits.

ii. Treated Analysis Set

The Treated Analysis Set includes follow up time contributed by each participant in the Treated Population and censors time in analysis for each woman at the earlier of the following: her estimated date of fertilization (EDF) (for women becoming pregnant), her last negative urine pregnancy test (for women who do not become pregnant), and the date that is 7 days after her last target visit date. In addition, The Treated Analysis Set excludes any follow-up time contributed by a woman when she was 8 to 28 days late for a re-injection.

> *For example, a woman who returns on week 20 rather than week 17 for her month 4 re-injection (i.e., 2 weeks past her 7-day grace period) but who returns precisely at 18-week intervals for her month 8 and final visit without becoming pregnant, would contribute 56 (20 + 18 +18) weeks to the Safety Analysis Set but only 54 (18 + 18 +18) weeks to the Treated Analysis Set.*

iii. Perfect use Analysis Set

The Perfect Use Analysis Set is a subset of the Treated Analysis Set, excluding any time during which a participant reported using another contraceptive method (including condoms) or drugs known to impact ovarian function or PK of MPA, unless she became pregnant in that period and the drug being used is known to only *increase* the risk of pregnancy among women using injectable DMPA. Exclusionary periods for prohibited drugs or contraceptive methods other than condoms will be determined based on the start and end dates provided on the corresponding concomitant medication form. If the end date is missing or indicated as ongoing, then all follow-up time after the reported start date will be excluded. Periods of exclusion for condom use will be determined based on a question with three options recorded on the FU CRF at each visit. If a participant reports using condoms in the last 4 weeks and at any other time since the last injection, then all time since the previous injection date will be excluded; if a participant reports using condoms since last injection but not in the last 4 weeks, then only the time between the previous injection date and the date which is 4 weeks prior to the report visit will be excluded; and if a participant

reports using condoms in the last 4 weeks but not at any other time since last injection, then only the last 4 weeks prior to the report visit will be excluded.

B. Pharmacokinetics Population and Analysis Set

The Pharmacokinetics (PK) Population is a subset of the Treated Population. The PK Population includes participants who agreed to serum MPA testing at 6 timepoints and were randomized into the PK cohort but excludes participants who did not contribute blood specimens for PK assessments, who had a baseline serum MPA concentration exceeding 0.05 ng/mL, or who required the use of more than one Sayana Press unit for their baseline injection (based on information provided on the injection CRF)[3]. The corresponding Pharmacokinetics Analysis Set will censor data collected after a participant receives an injection in an anatomical site which differs from the site used at enrollment and will exclude any MPA specimens collected during a time when a participant reports using a concomitant medication that may impact the PK of MPA as defined in the protocol. During the coding process, the medical monitor will define the length of the period of exclusion based on participants' use of concomitant medications on a medication-specific basis. The Analysis Set will also exclude MPA results from any blood samples collected after an injection where more than one Sayana Press unit was inserted into the participant's skin (i.e., if a participant had more than one unit inserted at her month 4 injection, then blood samples collected at months 8 and 12 would be excluded from the analysis set for that participant). PK analyses based on this analysis population will be performed according to the site of injection at enrollment, even if it was assigned or was received in error.

VI. Blind Review of Data

As indicated above, neither participants nor center staff will be blinded to injection sites. However, to the extent possible, decisions regarding additions or modifications to planned analyses, determination of exclusion from analysis populations or analysis sets, and rules for handling missing or incomplete data will be made by statisticians, clinicians, or other study staff who do not have access to individual treatment data. The actual level of blinding maintained when performing these activities will be described in the clinical study report.

VII. Analysis of Baseline Data

Baseline data will be presented for the Treated and PK Analysis Populations by injection site, study center, and pooled across injection sites and study center. Demographic and baseline characteristics, including medical history and concomitant medication use, will be provided in participant-specific listings and summarized using appropriate measures (frequencies and percentages for categorical data; means, standard deviations, standard errors, medians, minima, and maxima for continuous data). Differences in distributions of these characteristics

[3] At the time of injection, some Uniject devices were discovered to have malfunctioned after the needle had already been inserted into the participant's skin. In these cases, a second device was used. Because we cannot guarantee that no product was injected from the first device, we chose to exclude affected results.

between study centers will be assessed using exploratory analysis of variance for continuous variables and Fisher's Exact tests for categorical variables.

VIII. Analysis of Participant Disposition Data

Participant disposition data will be presented for the Treated and PK Analysis Populations, by injection site, study center, and pooled across injection sites and study centers. The numbers of participants screened, screened but not enrolled (including reason(s) not enrolled), randomized, treated (including reason(s) not treated, if any), and final status (e.g., early withdrawal (and reason), completed the study, etc.) will be summarized using frequencies and percentages. A diagram showing the flow of participants through the trial will be provided, as will a listing including study center, inclusion in the PK cohort, randomized injection site, actual injection site, final study status, and any other information that the study team determines to be relevant. Protocol violations will be provided in a listing and may also be summarized in a table using frequencies and percentages of violations falling into each of the categories given by the deviation code on the protocol violation form. The "other" violation category may be divided into additional categories if consistent themes appear.

IX. Analysis of Primary Study Objective

A. Primary Objective and Endpoint

The primary study objective is to evaluate the effectiveness of Sayana® Press when injected subcutaneously every 4 months in the abdomen or upper thigh for 12 months (3 treatment cycles) of use. The primary endpoint is the occurrence of pregnancy, as defined by a positive urine pregnancy test. Positive urine tests will be confirmed by ultrasound and/or serum hCG testing whenever possible. The EDF for each pregnancy will be calculated by a qualified study clinician based on ultrasound and last menstrual period (LMP) in accordance with the study Medical Monitoring Plan. In the absence of ultrasound or LMP, best clinical judgment will be used to estimate the EDF based on all available related information including but not limited to vaginal bleeding, patterns of coitus, and the timing of previous negative pregnancy test results.

Information on any pregnancies, miscarriages or abortions diagnosed outside the study center will be collected during follow-up interviews. Any such pregnancies with EDF determined to be within the treatment period will be included in the primary efficacy analysis unless the site investigator and study clinician unambiguously determine that the pregnancy diagnosis was incorrect and/or the self-reported data was unreliable.

B. Primary Efficacy Analysis

The primary efficacy analysis will be performed using the Treated Population[4] and the Treated Analysis Set. Recognizing the plus 7-day grace period for re-injections, pregnancies with an EDF

[4] Exclusion of participants from the primary efficacy analysis based on protocol violations occurring at enrollment (such as participant being enrolled while ineligible) will be considered on a case-by-case basis. A decision regarding inclusion of the participant will be made by the principle investigator in consult with the medical monitor and lead biostatistician. If possible, the decision will be made while these staff remain blinded to injection site and before

up to 18 weeks (126 days) after the first (enrollment) injection or up to 19 weeks (133 days) after subsequent re-injections will be included in the primary efficacy analysis.

The primary analysis of efficacy will be based on the pregnancy Pearl Index, defined as the number of pregnancies that occur during the treatment period per 100 women-years of time contributed to the Treated Analysis Set among women randomized to receive injections in the abdomen or thigh. Participants who do not become pregnant or who have EDFs that fall outside the windows used to define primary outcomes will be censored on the date of last negative urine pregnancy test or the end of the plus 7-day grace period since last injection, whichever is earlier. An exact 95% confidence interval for the Pearl Index will be computed based on an assumption that the number of pregnancies occurring in the treatment period follows a Poisson distribution. A listing of all participants who become pregnant during the study will include at least study center, randomized injection site, days on treatment until EDF, inclusion in the primary efficacy analysis, and pregnancy outcome.

C. Secondary Efficacy Analysis

Secondary efficacy analyses will include:

- Typical use life-table estimates of the cumulative probability of pregnancy through 3 treatment cycles, based on the Treated Population and Safety Analysis Set (excluding women randomized to receive injections in the upper arm). Point-wise 95% confidence intervals will be computed using the log-log transformation. For this analysis, the first, second and third treatment cycle can be up to 21, 22, and 22 weeks long, respectively (after accounting for up to a 28-day late period for re-injections or final study visit).
- An estimate of the Pearl Index computed based on the Perfect Use Analysis Set (excluding participants randomized to receive injections in the upper arm).
- An estimate of the Pearl Index based on the Treated Population and Safety Analysis Set (excluding participants randomized to receive injections in the upper arm). This estimate will include all follow-up time contributed (regardless of pregnancy status) and any pregnancies detected while participants are up to 28 days late for their visits.
- An estimate of the Pearl Index computed per the primary analysis, but including women randomized to receive injections in the upper arm.

In addition to the non-comparative analyses listed above, a Pearl Index based on the Treated Analysis Set will be computed separately for participants randomized to receive injections in the abdomen, thigh, and upper arm. Difference in pregnancy risk between groups will be assessed using a log-rank test stratified on study center. If pregnancy events are sufficiently rare so as to make this test inappropriate, this difference will be assessed using 95% confidence intervals for incident rate ratios based on Poisson distribution assumptions instead. If at least 5 pregnancies occur in one or more of the injection site groups, then the cumulative risk of pregnancy in each group will also be estimated using life-tables methods.

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results of any pregnancy tests are known for the participant in question. The actual level of blinding when decisions are made will be documented in future versions of the analysis plan or in the final report as appropriate.

X. Analysis of Secondary Study Objectives

The secondary study objectives are to assess the following when Sayana® Press is injected every 4 months for 12 months of use: 1) trough concentrations, accumulation, and apparent terminal half-life of MPA, and the impact of subcutaneous injection site (abdomen, upper thigh, or back of the upper arm) on these parameters, 2) the safety of Sayana® Press, and 3) the acceptability of Sayana® Press.

A. Pharmacokinetics of MPA

PK endpoints include serum MPA concentrations at baseline and months 2, 3, 4, 8, and 12. Post-baseline MPA concentrations that fall below the limit of quantification (LOQ) will be replaced by half the applicable LOQ. PK analyses will be performed using the PK Analysis Population and Set.

Serum MPA concentrations that fall within defined sampling windows (see Appendix A) will be summarized by timepoint and injection site in the following ways: 1) graphically using box plots with whiskers extending to 5th and 95th percentiles, and 2) in tables using means, geometric means, quartiles, minima, maxima, standard deviations, and percent coefficients of variation. A listing of all MPA concentrations for each participant will be provided along with an indication of any that fall outside of defined sampling windows, or any excluded from the PK Analysis Set due to concomitant medication use, injection in an anatomical site different from the site used at enrollment, or insertion of multiple Sayana Press units at the time of injection. The listing will also include subject age and BMI at time of sampling.

Month 2, 3, and 4 data will be used to estimate the apparent half-life for each injection site based on mixed-effects log-linear models with random intercept and slope terms, under the assumption that the terminal phase of absorption begins by month 2.[5] Unique variance components will be used for each injection site, and observations falling outside sampling windows will not be excluded. The estimated slope (m) for each injection site will be used to calculate the apparent half-life according to the following formula: $half\text{-}life = ln(2)/(-m)$. Pharmacokinetics in the terminal phase will be compared across injection sites based on overall and, if significant at the 0.05 level, pairwise Wald-type tests of differences in fixed-effects intercepts and slopes. Differences in variance components (both within-and between-subject effects) will similarly be assessed using likelihood ratio-tests.

Accumulation of MPA concentrations at months 8 and 12 will be estimated for each injection site by calculating the geometric mean ratio (GMR) of trough concentrations at 8 or 12 months to the trough concentration at 4 months, using mixed-effects models to compute 95% CIs of each GMR (with unspecified covariance of log-transformed repeated measures). Any MPA concentrations that are measured more than 7 days past a participant's scheduled injection date (along with any future measurements) will be excluded from the above accumulation

[5] This assumption will be formally assessed using appropriate log-linear random-effects model diagnostics, and by comparing predicted month 8 and month 12 concentrations (based on the half-life estimates and 4-month data) with the observed month 8 and 12 concentrations.

analysis. Steady-state accumulation ratios will be estimated as $R = [1-(0.5)^{\text{dosing interval/half-life}}]^{-1}$, where the dosing interval is assumed to be 126 days and the half-life is estimated in the method described above.

The effects of study center, BMI, and age on trough concentrations will be explored graphically and by incorporating covariates in mixed-effects models based on month 4, 8, and 12 data. Intra-subject variability across injection cycles may also be explored using MPA trough levels at months 4, 8, and 12.

B. Safety

Safety endpoints will include serious adverse events (SAEs), adverse events (AEs) leading to product withdrawal, injection site reactions, bleeding patterns, blood pressure, and body weight recorded at months 4, 8, and final visits. All SAEs, AEs leading to product withdrawal, and AEs which are Grade 1 or higher ISRs will be coded by a trained medical coder at FHI 360 using the Medical Dictionary for Regulatory Activities (MedDRA) to classify them according to preferred term and system organ class (SOC). Safety analyses will be performed using the Treated Population and Safety Analysis Set and will be based on treatment group actually received.

All relevant information on any SAEs will be discussed in the subject narrative included in any clinical study report and in a listing. Numbers and percentages of participants experiencing AEs (specifically AEs leading to product withdrawal and ISRs which are Grade 1 or higher) will be presented by severity, study center, and injection site. Percentages of participants experiencing specified AEs will be compared across injection sites (pooled over severity and study center) within each SOC using Fisher's exact tests. Listings of any AEs will include actual injection site, a description of AE, type of AE, days to onset, relatedness to Sayana Press, seriousness, severity, outcome, and duration. Numbers and percentages of participants experiencing ISRs of any grade will be summarized by injection site, and ISRs will also be presented in a listing.

Answers to questions about bleeding pattern (such as type of bleeding, average cycle length, duration of flow, and amount of flow) will be summarized by study center, injection site, and overall at enrollment, months 4 and 8, and final visit using appropriate measures (i.e., means, standard deviations, medians, minima, and maxima for continuous variables, and numbers and percentages for categorical ones). Blood pressure and body weight will also be summarized by study center, injection site, and overall at enrollment, months 4 and 8, and final visit using means, standard deviations, medians, minima, and maxima. Changes from baseline in bleeding patterns, blood pressure, and body weight at month 4, month 8, and final visit will also be summarized using shift-tables.

C. Acceptability

Acceptability endpoints include responses to questions about perception of bleeding patterns (recorded at enrollment, months 4 and 8, and final visit) and other side effects, likes, and dislikes about the regimen (recorded only at final visit). Acceptability will be assessed using the Treated Population and Safety Analysis Set. These will be summarized for each relevant visit by

study center, injection site, and overall using frequencies and percentages. Changes in perception of bleeding patterns over time will be summarized using shift-tables.

XI. Analysis of Exploratory Study Objective

Plans for analysis of the exploratory objective will be described in an appendix to this document.

XII. Additional Data Summaries

Any concomitant medications recorded at enrollment or during the study will be provided in a listing including at least the following information: participant number, actual injection site, generic name and dosage of medication, administration route, indication, days from enrollment to start date, and duration of use.

XIII. Sensitivity Analyses

Two sensitivity analyses will be performed for the efficacy objective. A Pearl Index and exact 95% confidence interval will be computed per the primary analysis (section IX.B) but excluding any women who had protocol violations occurring at enrollment that warrant exclusion based on blind review. Another Pearl Index and exact 95% confidence interval will be computed per the primary analysis but excluding results from pregnancy tests taken at home and any time between a participant's last in-clinic pregnancy test and her exit from the study. This will assess the impact of final pregnancy tests completed at home in response to the COVID-19 pandemic.

Two sensitivity analyses will be performed for the PK objective. The first will assess the impact of baseline MPA on PK profiles and will include all participants (except for those who required the use of more than one Sayana Press unit) in the PK cohort who provide samples for MPA testing. This will be done in the following way: calculate the half-life (λ) for each injection site using the same method described in the secondary objective above but using the revised population; use that half-life to calculate the concentration at time t (CB_t) due to the baseline amount (C_0) using the following formula

$$CB_t = C_0\, e^{-\lambda t};$$

then subtract that amount from the corresponding monthly concentrations for each participant. Summaries of trough concentrations will be provided using these modified values and population.

Secondly, a table summarizing trough concentrations and half-life will be provided for a population comprised of the PK Population plus any participants or samples excluded from the PK Population or Analysis Set based on injection issues (i.e., more than one unit inserted into skin).

XIV. Planned Interim Analyses

An independent DSMB will review interim data when approximately 250 participants have completed 18 weeks of follow-up. This single, pre-planned interim analysis is intended to inform a decision whether to stop or modify the study if the estimated probability of pregnancy pooled across all injection sites is greater than 2% in the first injection interval. Details are provided in a separate DSMB Operational Plan.

XV. MPA Testing of Baseline Serum Specimens

In preparation for the interim analysis, all available serum specimens from the PK cohort will be shipped for MPA testing at PPD approximately 8-10 weeks prior to the scheduled interim DSMB meeting. Once MPA results are received at FHI 360, baseline specimens will be analyzed to inform the following decision. If more than 10% of tested baseline specimens from the PK cohort have MPA concentrations greater than or equal to 0.1 ng/mL, or if more than 20% of tested baseline specimens from the PK cohort have MPA concentrations greater than or equal to 0.05 ng/mL, then the study team will proceed with MPA testing of all baseline specimens from the main cohort.

As soon as the decision is made to test baseline specimens from the main cohort (if applicable), all available baseline specimens from participants in the main cohort will be shipped to PPD for MPA testing. Once serum MPA results from this enrolled subset of the main cohort are received at FHI 360, baseline specimens will be analyzed to inform the following second decision. If more than 10% of tested baseline specimens from the main cohort have MPA concentrations greater than or equal to 0.1 ng/mL, or if more than 20% of tested baseline specimens from the main cohort have MPA concentrations greater than or equal to 0.05 ng/mL, then the study team will make a determination as to whether subjects with baseline levels exceeding a threshold should be excluded from the primary analysis, and initiate a discussion with the study funder surrounding the potential for expansion of enrollment to account for such exclusions. Specimens from the remainder of the main study cohort (enrolled after the first batch are shipped) will be sent to PPD for testing at a later time in order to inform any analysis decisions. Any analysis decisions made based on results of MPA testing of baseline specimens from main cohort participants will be made blind to pregnancy outcome results and will be recorded in future versions of the analysis plan or in the final report as appropriate.

XVI. Appendices

A. Visit Windows for MPA Measurements (PK Cohort Only)

Visit	Target Day (Window)	In-Window Range (inclusive)
Month 2	61 (+/-7)	54-68
Month 3	91 (+/-7)	84-98
Month 4	119 (+7)	119-126
Month 8*	245 (+7)	245-252
Month 12*	371 (+7)	371-378

*The target days for these visits will be shifted if a participant is more than 7 days (but less than 29 days) late for reinjection at the previous visit. If so, the target day(s) for the remaining visit(s) will be calculated in 126-day intervals after date of delayed reinjection (with the corresponding 7-day window). For example, if a participant comes in for her Month 4 visit on day 130, then her Month 8 target day (in-window range) becomes 256 (256-263) and her Month 12 target day (in-window range) becomes 382 (382-389).

B. Changes to the Analysis Plan after Approval of Version 1.0

i. Changes implemented in SAP version 2.0

- Updated randomization section to reference re-allocation of 100 participants to DR from Brazil due to slow recruitment at Brazil
- Added footnote clarifying how protocol violations at enrollment will be addressed within the primary efficacy analysis in section IX.B
- Added sensitivity analysis to assess efficacy after excluding women with protocol violations surrounding enrollment
- Added criteria for testing baseline specimens of MPA in the main study cohort based on results of baseline testing in the PK cohort
- Added possible exploratory analysis to look at intra-subject variability in trough levels across injection cycles

ii. Changes implemented in SAP version 3.0

- Added exploratory objective and endpoint per version 8.0-B of the protocol; added statement that analysis of this objective will be described separately
- Revised baseline and disposition tables to change summaries by injection site within study center to simply by study center
- Revised definition of PK Population and Analysis Set to exclude any time after relevant injections for participants whose provider was required to use more than one device to deliver the drug
- Moved previously defined sensitivity analysis in section IX.B to new section specifically for sensitivity analyses (XII)
- Defined one new sensitivity analysis for the efficacy objective around home pregnancy tests
- Defined two sensitivity analyses for the PK objective, based on baseline MPA concentrations and injection issues

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